



Malde, S., Fry, C., Schurch, B., Marcelissen, T., Averbek, M., Digesu, A., & Sahai, A. (2018). What is the exact working mechanism of botulinum toxin A and sacral neuromodulation in the treatment of overactive bladder / detrusor overactivity? ICI-RS 2017. *Neurourology and Urodynamics*, 37(S4), S108-S116.
<https://doi.org/10.1002/nau.23552>

Peer reviewed version

License (if available):
Unspecified

Link to published version (if available):
[10.1002/nau.23552](https://doi.org/10.1002/nau.23552)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Wiley at <https://onlinelibrary.wiley.com/doi/full/10.1002/nau.23552>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

What is the exact working mechanism of botulinum toxin A and sacral neuromodulation in the treatment of overactive bladder / detrusor overactivity? ICI-RS 2017

Sachin Malde¹, Christopher Fry², Brigitte Schurch³, Thomas Marcelissen⁴, Mario Aeverbeck⁵, Alex Digesu⁶, Arun Sahai^{1, 7}

1 Department of Urology, Guy's Hospital, London, UK

2 School of Physiology, Pharmacology & Neuroscience, University of Bristol, Bristol, UK

3 Department of Clinical Neurosciences, Neuropsychology and Neurorehabilitation Service
Vaudois University Hospital of Lausanne, Switzerland

4 Department of Urology, Maastricht University Medical Centre, Netherlands

5 Department of Urology, Moinhos de Vento Hospital, Brazil

6 Department of Urogynaecology, St. Mary's Hospital, UK

7 King's College London, King's Health Partners

Authors:

Mr Sachin Malde

Consultant Urological Surgeon,

Professor Christopher Fry

Chair in Applied Physiology & Head of School

Professor Brigitte Schurch

Specialist in Neurourology and Rehabilitation

Dr Thomas Marcelissen

Consultant Urologist

Dr Mario Averbek
Consultant Urologist

Dr Alex Digesu
Consultant Obstetrician & Gynaecologist

Mr Arun Sahai
Consultant Urological Surgeon & Honorary Senior Lecturer

Review Article
Word Count 3604 words

Correspondence to:
Arun Sahai
Consultant Urological Surgeon & Honorary Senior Lecturer
Guy's Hospital, London, SE1 9RT
Email: arun.sahai@gstt.nhs.uk

Disclosures / Conflicts of Interest

SM

CF

BS

TM

MA

AD

AS – Unrestricted educational grant – Allergan, Speaker fees Allergan, Pfizer, Astellas, Trial
Investigator – Allergan, AMS, Astellas

Abstract

Aims: Botulinum toxin A (BTX-A) and sacral neuromodulation (SNS) are well established treatments for overactive bladder (OAB) and appear as standard of care in refractory cases in many international urological guidelines related to the subject. Despite long term use over decades their 'exact' working mechanisms are not entirely clear. At the ICI-RS meeting in Bristol in 2016 a think tank was convened to address the question. **Methods:** The think tank conducted a literature review and an expert consensus meeting focussing on current established mechanisms and what could be learned from clinical experience and objective urodynamic data. **Results:** Clinical and urodynamic results with BTX-A suggests effects on both filling and voiding parts of the micturition cycle. The salient data in this regard is presented as well as additional studies related to the urothelium and evidence for more central effects. Urodynamics have shown consistently increases in cystometric, bladder compliance and reductions in detrusor pressures during filling, however post void residuals also increase in a dose dependent fashion. During SNM activation of somatic afferent nerves inhibits bladder sensory pathways and reflex bladder hyperactivity. Evidence in the cat model suggests the inhibition of bladder activity occurs primarily in the CNS by inhibition of the ascending or descending pathways of the spinobulbospinal micturition reflex. Urodynamics have suggested improvement in filling phase such as increases in cystometric capacity and reduction in detrusor pressures during filling with little observed effects on voiding parameters. **Conclusions:** The working mechanism of BTX-A and SNS is complex. The exact mechanisms are still unknown, although considerable progress has been made in our understanding. Further research proposals are suggested to help further elucidate these mechanisms.

Keywords: botulinum toxin, OnabotulinumtoxinA, sacral neuromodulation, sacral nerve stimulation, Botox, Interstim, overactive bladder, detrusor overactivity, mechanism of action, urodynamics

Introduction

Recent long term, high volume, prospective trials have confirmed the efficacy and durability of both Botulinum Toxin-A (BTX-A) and sacral neuromodulation (SNM) in treating idiopathic overactive bladder (OAB)^{1,2}. Despite the mainstream use of both BTX-A and SNM worldwide in treating OAB, the exact mechanisms of action of both treatments are poorly understood. At the ICI-RS meeting in Bristol in 2017, a think tank was convened to answer the question “Do we know the exact working mechanisms of BTX-A and SNM in the treatment of OAB/detrusor overactivity (DO)?” Although the likely answer is ‘no’, the think tank discussed new mechanisms related to both treatments and tried to correlate modes of action with some clinical perspectives. Finally, we decided to assess urodynamic data before and after these treatments to see if we could glean any further information that could help us understand their mode of action. The think tank discussed future research strategies to help answer the question and advance knowledge, this will be summarised at the end of the manuscript.

Methods

The literature on BTX-A and SNM was reviewed through PubMed searches, restricted to articles published in English. Articles were screened based on titles and abstracts and the most relevant articles included. The focus was related to mechanism of action and urodynamic data.

Pathophysiology of OAB

To understand the effects of SNM and BTX-A in OAB patients, it is important to summarise briefly the proposed pathophysiological mechanisms related to storage symptoms. Several theories, alone or in combination, have been proposed to explain the origin of OAB³⁻⁹.

Dysfunction of Afferent Signaling in OAB

OAB may be a result of increased, abnormal afferent activity, resulting in increased reflex efferent signaling. Consequently, voluntary control of micturition is compromised³.

Altered Brain Responses

OAB patients present abnormal brain responses in areas processing urge and social propriety^{4,5}. Alternatively, there might be diminished responses in areas responsible for voluntary voiding. According to functional magnetic resonance imaging (f-MRI), poor bladder control is specifically associated with inadequate activation of the orbitofrontal cortex.

Myogenic Theory

Partial denervation alters smooth muscle properties, which may result in increased excitability, coordinated myogenic contractions and augmented bladder pressure⁶.

Neurogenic-Myogenic Theory

'Leakage' of Acetylcholine (ACh) from parasympathetic nerves during bladder filling may be related to micromotion of detrusor bundles and afferent activation^{7,8}.

Urothelial Theory

Several compounds (e.g. acetylcholine, ATP, nitric oxide, prostaglandins) are released and/or generated by urothelial cells and are related to cell signaling events⁹.

BTX-A

Mechanism of action

Chemical transmission and botulinum toxins. Chemical transmission between cells generally consists of transmitter release from a prejunctional cell, diffusion in the intercellular space and subsequent binding to the cell membrane of a post-junctional cell where it generates a response. Classically this process was described at the neuromuscular junction, where acetylcholine (ACh) released from motor nerves binds to skeletal muscle nicotinic receptors to initiate muscular

contraction. However, transmission between any combination of nerves, skeletal/cardiac/smooth muscle, epithelial and other cell types is possible. Transmitters are generally, but not exclusively, stored in prejunctional intracellular vesicles and released when they dock to the cell membrane and exocytose their contents. Docking is achieved by interaction between SNARE proteins located on the cell membrane and vesicles. Botulinum toxins, from *Clostridium botulinum* bacteria, prevent transmitter release by inhibiting vesicular docking. There are several subtypes (A–G) that cleave different docking proteins. The subtype used most commonly in urological practise, BTX-A, acts on a membrane docking protein SNAP-25. Botulinum toxins are taken into the cell upon binding to a receptor site, SV-2, where they are subsequently cleaved into light and heavy chains so that the former can exert its effect¹⁰.

OAB and BTX-A. The original rationale for using BTX-A to reduce OAB was the assumption that OAB itself was importantly caused by aberrant release of ACh from parasympathetic efferents to cause DO, in much the same way as antimuscarinic agents were assumed to inhibit the activity of this ACh in detrusor smooth muscle. With human detrusor from overactive bladders ACh and ATP are functional co-transmitters at the nerve-muscle junction, but this would not affect the basic premise as ACh and ATP release were equally attenuated by BTX-A¹¹.

Since then the cause of OAB/DO has undergone considerable re-evaluation to also include a myogenic origin of spontaneous activity; a direct control of detrusor contractile function by the overlying mucosa; and augmentation of afferent activity by the mucosa to enhance an afferent-CNS-efferent loop^{12,13}. To accommodate these new theories a greater understanding of the action of BTX-A is needed.

BTX-A and bladder function. A reduction of maximum detrusor pressure, P_{det} , would be expected through any mode of action for BTX-A and has been reported for adults and children with neurogenic or idiopathic DO¹⁴⁻¹⁷. However, an increase of compliance has also been reported that implies an additional action in the filling phase^{15,17}. The time course for changes to P_{det} and compliance were similar¹⁷ but does not imply a common mode of action. Such changes to P_{det} ,

and compliance were not discernible in a mouse model with intraluminal application of BTX-A (2U/bladder)¹⁸. The latter study did record a significant reduction of afferent nerve firing on filling that was independent of detrusor pressure during filling or voiding. Furthermore, the attenuation of firing rate was observed in high and low threshold fibres. The study suggested either that nerve excitability itself was reduced by BTX-A and/or the transduction mechanism that links bladder filling to afferent firing had a lower gain.

There is increasing evidence that also supports an effect of BTX-A on purinergic pathways, especially those involved in bladder pathophysiology such as DO^{19,20}. Controversies remain about the origin of the decreased detrusor pressure e.g. inhibition of the exocytosis of ACh versus decreased expression of muscarinic receptors^{21,22}. In a guinea pig model, cleaved SNAP-25 (an indirect marker of a BTX-A effect) products were seen at 24 hours and were expressed in 85% of vesicular ACh Transporter positive cholinergic fibres (parasympathetic) and in 42% and 36% of tyrosine hydroxylase positive adrenergic (sympathetic) and calcitonin gene related peptide positive (sensory) fibres, respectively. This suggested indirectly that the BTX-A mode of action is apparent at both motor and sensory neurones²³.

BTX-A and urothelial function. The urothelium has been proposed to provide a vital link between stressors, such as stretch of the bladder wall during filling or exposure to noxious agents, and afferent activation through the release of neuromodulators such as ATP, ACh, nitric oxide (NO) and prostaglandins²⁴⁻²⁶. Moreover, there is an increase of stressor-induced ATP release in pathologies associated with OAB²⁷. This raises the possibility that BTX-A attenuates stretch-activated modulator release and therefore diminishes afferent firing. Such a mechanism could also explain the action of BTX-A to increase bladder compliance, especially when pathologically raised. ATP release from urothelium is, at least in part via a vesicular route^{28,29} and the molecular apparatus for BTX-A uptake in urothelial cells is present through identification of SV2 and SNAP isoforms²⁰. Moreover, BTX-A reduces stretch-activated ATP release from the bladder *in vivo*¹⁸, and from urothelial cells *in vitro*^{20,30} to provide the link between its ability to increase bladder compliance and reduce afferent firing. ACh release from urothelium has been studied less, but is

released in greater quantities and more readily than ATP and there is evidence it has a paracrine/autocrine action to regulate urothelial ATP release via an M2 receptor³¹, Figure 1. However, release of ACh from urothelial cells is not vesicular^{25,31}, in large part via a CFTR channel and BTX-A has no effect on urothelial ACh release *in vitro*³¹ or *in vivo*¹⁸. It is also of interest BTX-A treatment increases NO release from the bladder wall of normal animals¹⁸, or from urothelial cells of animals with spinal cord injury³⁰. As NO is a muscle relaxant its modulation by BTX-A may contribute to its effects on voiding detrusor pressure or filling compliance. The mechanism remains to be characterised.

Overall, changes to *in vivo* human bladder function after BTX-A administration indicate additional effects to its attenuation of transmitter release from efferent nerves. As more is understood about the neuromodulatory actions of the urothelium so too does the emphasis shift for a major action of BTX-A on the bladder, away from its modulation of vesicular ACh and ATP release at the nerve-muscle function to vesicular ATP urothelial release.

Central effects. In a rat model, BTX-A or normal saline were injected intrathecally into either spinal cord transected rats or sham-operated controls³². Spinal cord injury increased basal bladder pressure and frequency of contractions when compared to controls and the administration of BTX-A, unlike normal saline, significantly attenuated contraction frequency and reduced baseline pressures towards normal: no animals receiving BTX-A went into urinary retention. Cleaved SNAP-25 was seen in the superficial dorsal horn of lumbosacral segments in BTX-A treated SCI rats, an area where most of the sensory nerves terminate. Cleaved SNAP-25 was not detected in preganglionic parasympathetic or motor neurons. Furthermore, BTX-A reduced the intensity of CGRP immunoreactivity at L5/6 to values comparable to those observed in spinal intact animals. These data were interpreted that BTX-A significantly impaired sensory fibres through a mechanism involving cleavage of SNAP-25 at terminals in the spinal cord dorsal horn³². Further evidence supporting central effects was the observation in rats of retrograde transport of BTX-A after bladder injection³³. BTX-A was radiolabelled with technetium-99 and was detected in the dorsal root ganglia 6 hrs post-injection and corresponding to about 3% of the injected dose into the bladder.

Clinical perspectives on BTX-A that help to understand mechanisms of action

OnabotulinumtoxinA (Botox, Allergan Ltd, Irvine, CA) received a license to treat both neurogenic detrusor overactivity (NDO) at 200 U, secondary to multiple sclerosis and spinal cord injury, and idiopathic OAB at 100 U in 2011 and 2013, respectively. In 2000, Schurch first described the use of BTX-A to treat NDO in spinal cord injured patients, who suffered from urinary incontinence between two intermittent self-catheterisations despite high dosages of anticholinergic drugs³⁴. These patients had a significant reduction of urinary incontinence, with decreased reflex volumes and increased maximum cystometric capacity (MCC). It was believed that the principal mechanism of action in NDO was its effect on efferent parasympathetic pathways. This might be true in part, as during the urodynamic voiding phase post BTX-A treatment reduced P_{detmax} and post void residual (PVR) increased. However, urodynamic data also showed a significant increase of maximum cystometric capacity (MCC) and the disappearance of uninhibited bladder contractions, and more importantly patients reported a significant benefit from urgency through their bladder diaries, none of which could be explained by efferent blockade alone. Subsequently a significant reduction in suburothelial P2X₃ and TRPV₁-positive fibres was demonstrated at 4 weeks after BTX-A, and more significantly at 16 weeks in bladder biopsies from patients suffering from NDO and treated with BTX-A³⁵. P2X₃ fibre reduction was significantly correlated to attenuation of urgency episodes at 4 and 16 weeks but not to maximum cystometric capacity or detrusor pressures, with a similar trend for TRPV₁, suggesting a sensory mechanism.

Repeated BTX-A injections are required as effects diminish, but are equally efficacious in OAB and NDO with mean duration of effect of 7.6 and 9.0 months, respectively for 100 and 200 U^{1,36}. Seroconversion, the presence of toxin neutralising antibodies, was very low but dose-dependent; 0.4% for 150 U in OAB¹ and 1.5% for 200 U in NDO³⁶. In seroconverted patients their request for further injections was sooner than those that had not seroconverted (4.9 vs 9.1 months)³⁶.

Sacral Neuromodulation (SNM)

SNM is an established alternative for treatment of overactive bladder symptoms in patients who failed previous therapies. Although its mechanism of action is not completely understood, several studies have demonstrated its efficacy and durability^{2,37,38}. Continuous improvements have been introduced and it is now a minimally invasive technique, performed under local anesthesia, and might be considered before invasive reconstructive procedures. Briefly, an electrode is implanted in the S3 foramen and connected to an implantable pulse generator (IPG). The patient undergoes a test phase lasting for days to weeks to determine whether SNM has provided a relevant benefit. If results are positive, the IPG is implanted in the upper buttocks³⁹. At present, InterStim® Therapy (Medtronic, Minneapolis, MN, USA) is licensed for treatment of chronic non-obstructive urinary retention and symptoms of OAB, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, or in patients with idiopathic lower urinary tract dysfunction who have failed or could not tolerate more conservative treatments⁴⁰.

SNM Mechanism of Action

The goal of SNM is to modulate abnormal sensations and involuntary reflexes of the lower urinary tract and restore voluntary control. SNM therapeutic benefits may arise from the effects of electrical stimulation on afferent and efferent nerve fibres connecting the pelvic viscera, and spinal interneurons to the central nervous system. SNM influences sacral afferents and modulates spinal cord reflexes and brain centres involved in lower urinary tract function³⁷. Thus, patients whose neural system is not intact may not be ideal candidates for this therapy⁴¹.

The stimulator provides an electrical charge to an area near the sacral nerve, resulting in altered neural activity. This stimulation depolarises the nerve, generating an action potential which propagates along the axon. SNM electrically stimulates somatic afferent nerves in a sacral spinal root and sends signals to the CNS that may restore normal bladder function. Activation of somatic afferent nerves inhibits bladder sensory pathways and reflex bladder hyperactivity³. Unlike other therapies that target the bladder directly, this approach does not directly influence the bladder or

sphincter muscles^{42,43}. The maximal effect of neuromodulation is not directly attained, indicating that neuromodulation induces adaptive changes (i.e. neural plasticity). This could be caused by negative modulation of excitatory synapses in the central micturition reflex pathway⁴². Evidence from cats suggests that reduction of bladder activity occurs primarily in the CNS by inhibition of the ascending or descending pathways of the spinobulbospinal micturition reflex⁴⁴. However, experiments show that SNM delivers graded responses dependent on stimulus protocols⁴⁵⁻⁴⁷. The inhibitory effects on bladder contraction may be mediated by both afferent and efferent mechanisms. Lower intensities of stimulation may activate large, fast-conducting fibres acting through the afferent limb of the micturition reflex arc in SNM. Higher intensities may additionally act through the efferent limb⁴⁵.

The effects of acute electrical stimulation frequency and amplitude on the dorsal nerve of the penis (DNP), pudendal nerve (PN) and S1 sacral nerve on isovolumetric reflex bladder contractions and maximum cystometric capacity was studied in anaesthetised cats⁴⁶. There was no significant difference in the maximum extent to which the optimised frequency or amplitude inhibited bladder contractions or increased cystometric capacity. However, the range of amplitudes and frequencies for maximum inhibition was larger for DNP stimulation than for PN or S1 stimulation⁴⁶.

Three rate-setting sequences have been tested in OAB female patients undergoing SNM: 5.2, 14 and 25 Hz⁴⁷. There were significant effects on the number of incontinence episodes and pad changes per day. At 5.2 Hz there were more incontinence episodes and pad changes than at 14 or 25 Hz. The number of adverse events was similar across the three rate settings, but programming-related adverse events were lowest in the 14 Hz group⁴⁷.

Can we gain valuable information on the mechanism of action of BTX-A and SNS from urodynamic or other tests?

Patient selection is a key factor in achieving optimal clinical outcomes with BTX-A and SNM. Clinical factors, such as severity of urge incontinence episodes, age, and comorbidity may help to guide treatment choice^{48,49}. However, improving our understanding their mechanism of action may provide a more satisfactory way to guide patient selection, and urodynamic studies may prove valuable in this regard in identifying predictive factors for success and complications.

BTX-A. Results on the effect of intravesical injections of BTX-A on urodynamic variables supports the hypothesis that it has both afferent and efferent mechanisms of action in OAB. A randomised placebo-controlled study in idiopathic OAB showed a dose-dependent improvement of mean cystometric capacity, with 100 U leading to a mean improvement by 71 ml at 12-week follow-up⁵⁰. Improvements in the mean volume at first involuntary detrusor contraction by 83 ml with 100 U also confirm its effect on the afferent micturition pathway. A systematic review of studies also showed consistent improvements in filling-phase parameters of mean maximum cystometric capacity and maximum detrusor pressure following BTX-A injection of 32% and -31%, respectively⁵¹. The presence or absence of DO has been shown in several studies not to influence the outcome as assessed by patient-reported outcome measures. However, this may be due to limitations in assessment, as these studies were based on standard cystometry which itself has a poor negative predictive value in diagnosing DO⁵². To more accurately determine whether the presence and severity of DO is a predictor of poor outcome, future studies should be undertaken using ambulatory urodynamics.

Urodynamic findings pre-and post-injection in five patients who did not respond to BTX-A injections for idiopathic DO have been reviewed⁵³. Baseline maximum detrusor pressure during filling of greater than 110 cmH₂O had a sensitivity and specificity of 86% and 100%, respectively, in predicting a poor response to treatment. However, future study in a larger cohort of patients is warranted to validate these findings. The effect of BTX-A on voiding urodynamic parameters have

not been well-studied in large randomised-controlled trials. However the urodynamic voiding parameters in 67 patients treated with 200U of BTX-A have been reviewed and it was found that patients requiring clean intermittent self-catheterisation (CISC) had a lower baseline Q_{max} and detrusor contractility⁵⁴. A projected isovolumetric pressure (PIP1) of ≤ 50 cmH₂O in women (sensitivity 83%; specificity 70%) and bladder contractility index (BCI) ≤ 120 in men (sensitivity 70%; specificity 79%) predicted the need for CISC. More recently, the outcomes of 290 patients treated with BTX-A for OAB have been reviewed, where it was found that a voiding efficiency of $< 89\%$ ((voided volume/total bladder capacity) X100) was a predictor of a high post-void residual (> 200 ml)⁵⁵. However, these studies were limited by their sample size and retrospective nature. Larger prospective studies of filling and voiding parameters are required to identify predictive factors for poor outcomes and the need for CISC, to aid patient counselling and selection.

An alternative drug delivery technique using BTX-A encapsulated in liposomes has been trialled in a double-blind randomised-controlled trial, with significant improvements in frequency and urgency and no increased risk of urinary retention compared to placebo⁵⁶. Urodynamic variables were not assessed in this study but in a preliminary animal study a significant reduction in inter-contraction interval was measured, with no effect on voiding detrusor contraction strength suggesting an afferent effect without significant efferent response⁵⁷. Further studies of alternative drug delivery techniques (liposomes/electromotive drug administration) should include a urodynamic assessment of storage and voiding function.

SNS. A study analysing pre and post-operative urodynamic findings in 33 women with IDO reported improvements in filling-phase parameters of median maximum detrusor pressure (29% reduction), median amplitude of the highest involuntary detrusor contraction (24% reduction), and maximum cystometric capacity (33% improvement) at 6 months after implantation⁵⁸. However, effects on the voiding parameters of urethral resistance and bladder contraction strength were not significantly different compared to baseline. This may suggest that SNM does not have a direct role in the

efferent arm of the micturition reflex, and rather affects voiding function through a different, possibly central, mechanism. This has also been suggested by neurophysiological studies using EEG recordings during SNM by S3 stimulation, which showed increased activity in the sensory cortex⁵⁹. Another study of 19 women who underwent SNM for OAB highlighted a potential role for urethral function in its mode of action⁶⁰. Urethral instability (defined as urethral pressure variations of more than 15 cmH₂O) disappeared in 54% of successfully treated patients, a change that was not seen for DO. Furthermore, 84% of patients had urethral pressure fluctuations of >30 cmH₂O prior to treatment, but this was seen in only 29% following implantation. Again, significant improvements were seen in mean volume at first sensation (from 98 ml to 235 ml) and mean peak detrusor pressure during filling (from 42 cmH₂O to 25 cmH₂O), and has been confirmed by others⁶¹. Another study of 54 patients confirmed the effects of SNM on filling-phase parameters, with improvements in mean bladder volume at first sensation by 57% and maximum cystometric capacity by 29%. As is the case with studies on BTX-A, the presence of DO has no influence on the clinical success of SNM⁶². These findings have been confirmed in other studies with similar magnitudes of effect⁶³. When ambulatory urodynamics were assessed before and after SNM, there was no significant difference in the maximum amplitude of detrusor contraction or number of detrusor contractions, but the detrusor activity index (DAI) correlated significantly with clinical success⁶⁴.

The use of neurophysiological testing of somatosensory evoked potentials (SEP's) of the pudendal and posterior tibial nerves has shown that the mechanism of action of SNM is via afferent pathways at the cortical level, and preliminary evidence suggests that the pattern of SEP and its modification by SNM could be used as a predictive factor of successful clinical outcome⁶⁵. This promising finding needs to be reproduced to determine its clinical utility.

Conclusions

The exact working mechanisms of BTX-A and SNM are complicated and are currently not fully known, but a considerable amount of research has yielded information about potential mechanisms. BTX-A appears to have both motor and sensory effects as seen in clinical practice

and further evidenced by urodynamic data, human biopsy work and animal models. SNM is likely to modulate abnormal sensory signaling and to correct any imbalance seen between sensory and motor signaling related to the bladder. Further research into the working mechanisms of these treatments will help us further understand the working mechanisms of BTX-A and SNM but also provide further insights into the pathophysiology of OAB.

Research Proposals

BTX

- Further research to expand on central effects and confirmation of retrograde transport to DRGs and CNS in OAB / DO
- Further explore the role of the urothelium and the exact mechanisms involved of BTX-A at this level
- Effect on signaling in suburothelium and interstitial cells and mechanism of action on sensory nerves
- More human bladder tissue orientated research
- Explore the effect of BTX-A at time of clinical relapse
- Explore the possibility of modifying BTX-A such that its effects are on sensory nerves in isolation
- Liposome / Lipotoxin / other strategies to breach the urothelium and allow BTX-A delivery into the bladder wall
- Bladder based injections only – large scale study to ascertain if the beneficial effects of the toxin can be maintained whilst keeping voiding dysfunction to a minimal
- Analysis of poor responders to BTX-A to ascertain reason why
- Ambulatory urodynamic studies pre and post injection may help to identify stronger predictive factors for success of BTX-A
- Larger prospective studies of urodynamic and contractility parameters are required to identify predictive factors for poor outcomes and need for CISC

SNS

- Comparison of tibial nerve vs pudendal vs SNM mechanisms of action
- Parallels drawn from mechanisms of SNM for bowel dysfunction
- Central effects of SNM as characterised by next generation fMRI studies
- Which patient factors determine success in SNM?

- Can combination of SNM and pharmacotherapy (e.g. antimuscarinics, mirabegron, opioids) increase efficacy?
- What is the onset/offset of action in SNM?
- Alteration of stimulation parameters – frequency, cycling and impact on efficacy
- Further research into SNM for NDO and in particular in acute SCI
- Larger prospective studies comparing outcomes of SNM vs BTX-A in terms of urodynamic parameters
- Whether ambulatory urodynamic parameters, such as the DAI, can predict success in SNM
- Further evaluation of neurophysiological tests, such as somatosensory evoked potentials, are needed to answer the following questions: do they correlate with clinical outcome? Can they be used as predictive factors? Can they help determine optimal stimulation parameters for SNM

References

1. Nitti, V. W., Ginsberg, D., Sievert, K. D. et al.: Durable Efficacy and Safety of Long-Term OnabotulinumtoxinA Treatment in Patients with Overactive Bladder Syndrome: Final Results of a 3.5-Year Study. *J Urol*, **196**: 791, 2016
2. Siegel, S., Noblett, K., Mangel, J. et al.: Five-Year Followup Results of a Prospective, Multicenter Study of Patients with Overactive Bladder Treated with Sacral Neuromodulation. *J Urol*, 2017
3. Leng, W. W., Morrisroe, S. N.: Sacral nerve stimulation for the overactive bladder. *Urol Clin North Am*, **33**: 491, 2006
4. Griffiths, D., Tadic, S. D.: Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. *Neurourol Urodyn*, **27**: 466, 2008
5. Griffiths, D., Derbyshire, S., Stenger, A. et al.: Brain control of normal and overactive bladder. *J Urol*, **174**: 1862, 2005
6. Turner, W. H., Brading, A. F.: Smooth muscle of the bladder in the normal and the diseased state: pathophysiology, diagnosis and treatment. *Pharmacol Ther*, **75**: 77, 1997
7. Andersson, K. E.: Treatment-resistant detrusor overactivity--underlying pharmacology and potential mechanisms. *Int J Clin Pract Suppl*: 8, 2006
8. Drake, M. J., Harvey, I. J., Gillespie, J. I. et al.: Localized contractions in the normal human bladder and in urinary urgency. *BJU Int*, **95**: 1002, 2005
9. Keay, S. K., Birder, L. A., Chai, T. C.: Evidence for bladder urothelial pathophysiology in functional bladder disorders. *Biomed Res Int*, **2014**: 865463, 2014
10. Jiang, Y. H., Liao, C. H., Kuo, H. C.: Current and potential urological applications of botulinum toxin A. *Nat Rev Urol*, **12**: 519, 2015
11. Lawrence, G. W., Aoki, K. R., Dolly, J. O.: Excitatory cholinergic and purinergic signaling in bladder are equally susceptible to botulinum neurotoxin a consistent with co-release of transmitters from efferent fibers. *J Pharmacol Exp Ther*, **334**: 1080, 2010
12. Birder, L. A., Andersson, K. E., Kanai, A. J. et al.: Urothelial mucosal signaling and the overactive bladder-ICI-RS 2013. *Neurourol Urodyn*, **33**: 597, 2014
13. Hanna-Mitchell, A. T., Kashyap, M., Chan, W. V. et al.: Pathophysiology of idiopathic overactive bladder and the success of treatment: a systematic review from ICI-RS 2013. *Neurourol Urodyn*, **33**: 611, 2014
14. Chen, G., Liao, L.: Injections of Botulinum Toxin A into the detrusor to treat neurogenic detrusor overactivity secondary to spinal cord injury. *Int Urol Nephrol*, **43**: 655, 2011
15. Game, X., Mouracade, P., Chartier-Kastler, E. et al.: Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *J Pediatr Urol*, **5**: 156, 2009
16. Kanagarajah, P., Ayyathurai, R., Caruso, D. J. et al.: Role of botulinum toxin-A in refractory idiopathic overactive bladder patients without detrusor overactivity. *Int Urol Nephrol*, **44**: 91, 2012
17. Klaphajone, J., Kitisomprayoonkul, W., Sriplakit, S.: Botulinum toxin type A injections for treating neurogenic detrusor overactivity combined with low-compliance bladder in patients with spinal cord lesions. *Arch Phys Med Rehabil*, **86**: 2114, 2005
18. Collins, V. M., Daly, D. M., Liaskos, M. et al.: OnabotulinumtoxinA significantly attenuates bladder afferent nerve firing and inhibits ATP release from the urothelium. *BJU Int*, **112**: 1018, 2013
19. Khera, M., Somogyi, G. T., Kiss, S. et al.: Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. *Neurochem Int*, **45**: 987, 2004
20. Hanna-Mitchell, A. T., Wolf-Johnston, A. S., Barrick, S. R. et al.: Effect of botulinum toxin A on urothelial-release of ATP and expression of SNARE targets within the urothelium. *Neurourol Urodyn*, **34**: 79, 2015
21. Smith, C. P., Franks, M. E., McNeil, B. K. et al.: Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. *J Urol*, **169**: 1896, 2003

22. Schulte-Baukloh, H., Priefert, J., Knispel, H. H. et al.: Botulinum toxin A detrusor injections reduce postsynaptic muscular M2, M3, P2X2, and P2X3 receptors in children and adolescents who have neurogenic detrusor overactivity: a single-blind study. *Urology*, **81**: 1052, 2013
23. Coelho, A., Cruz, F., Cruz, C. D. et al.: Spread of onabotulinumtoxinA after bladder injection. Experimental study using the distribution of cleaved SNAP-25 as the marker of the toxin action. *Eur Urol*, **61**: 1178, 2012
24. Ferguson, D. R., Kennedy, I., Burton, T. J.: ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes--a possible sensory mechanism? *J Physiol*, **505 (Pt 2)**: 503, 1997
25. Hanna-Mitchell, A. T., Beckel, J. M., Barbadora, S. et al.: Non-neuronal acetylcholine and urinary bladder urothelium. *Life Sci*, **80**: 2298, 2007
26. Tanaka, I., Nagase, K., Tanase, K. et al.: Modulation of stretch evoked adenosine triphosphate release from bladder epithelium by prostaglandin E(2). *J Urol*, **185**: 341, 2011
27. Fry, C. H., Vahabi, B.: The Role of the Mucosa in Normal and Abnormal Bladder Function. *Basic Clin Pharmacol Toxicol*, **119 Suppl 3**: 57, 2016
28. Birder, L. A., Barrick, S. R., Roppolo, J. R. et al.: Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. *Am J Physiol Renal Physiol*, **285**: F423, 2003
29. McLatchie, L. M., Fry, C. H.: ATP release from freshly isolated guinea-pig bladder urothelial cells: a quantification and study of the mechanisms involved. *BJU Int*, **115**: 987, 2015
30. Smith, C. P., Gangitano, D. A., Munoz, A. et al.: Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. *Neurochem Int*, **52**: 1068, 2008
31. McLatchie, L. M., Young, J. S., Fry, C. H.: Regulation of ACh release from guinea pig bladder urothelial cells: potential role in bladder filling sensations. *Br J Pharmacol*, **171**: 3394, 2014
32. Coelho, A., Oliveira, R., Cruz, F. et al.: Impairment of sensory afferents by intrathecal administration of botulinum toxin A improves neurogenic detrusor overactivity in chronic spinal cord injured rats. *Exp Neurol*, **285**: 159, 2016
33. Papagiannopoulou, D., Vardouli, L., Dimitriadis, F. et al.: Retrograde transport of radiolabelled botulinum neurotoxin type A to the CNS after intradetrusor injection in rats. *BJU Int*, **117**: 697, 2016
34. Schurch, B., Schmid, D. M., Stohrer, M.: Treatment of neurogenic incontinence with botulinum toxin A. *N Engl J Med*, **342**: 665, 2000
35. Apostolidis, A., Popat, R., Yiangou, Y. et al.: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol*, **174**: 977, 2005
36. Kennelly, M., Dmochowski, R., Schulte-Baukloh, H. et al.: Efficacy and safety of onabotulinumtoxinA therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: Final results of a long-term extension study. *Neurourol Urodyn*, **36**: 368, 2017
37. Bernstein, A. J., Peters, K. M.: Expanding indications for neuromodulation. *Urol Clin North Am*, **32**: 59, 2005
38. Hassouna, M. M., Siegel, S. W., Nyeholt, A. A. et al.: Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. *J Urol*, **163**: 1849, 2000
39. Thompson, J. H., Sutherland, S. E., Siegel, S. W.: Sacral neuromodulation: Therapy evolution. *Indian J Urol*, **26**: 379, 2010
40. Gormley, E. A., Lightner, D. J., Faraday, M. et al.: Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. *J Urol*, **193**: 1572, 2015
41. Kessler, T. M., Wöllner, J., Kozomara, M. et al.: [Sacral neuromodulation for neurogenic bladder dysfunction]. *Urologe A*, **51**: 179, 2012

42. van der Pal, F., Heesakkers, J. P., Bemelmans, B. L.: Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction. *Curr Opin Urol*, **16**: 261, 2006
43. Chancellor, M. B., Chartier-Kastler, E. J.: Principles of Sacral Nerve Stimulation (SNS) for the Treatment of Bladder and Urethral Sphincter Dysfunctions. *Neuromodulation*, **3**: 16, 2000
44. Zhang, F., Zhao, S., Shen, B. et al.: Neural pathways involved in sacral neuromodulation of reflex bladder activity in cats. *Am J Physiol Renal Physiol*, **304**: F710, 2013
45. Su, X., Nickles, A., Nelson, D. E.: Optimization of Neuromodulation for Bladder Control in a Rat Cystitis Model. *Neuromodulation*, **19**: 101, 2016
46. Snellings, A. E., Grill, W. M.: Effects of stimulation site and stimulation parameters on bladder inhibition by electrical nerve stimulation. *BJU Int*, **110**: 136, 2012
47. Peters, K. M., Shen, L., McGuire, M.: Effect of Sacral Neuromodulation Rate on Overactive Bladder Symptoms: A Randomized Crossover Feasibility Study. *Low Urin Tract Symptoms*, **5**: 129, 2013
48. Richter, H. E., Amundsen, C. L., Erickson, S. W. et al.: Characteristics Associated with Treatment Response and Satisfaction in Women Undergoing OnabotulinumtoxinA and Sacral Neuromodulation for Refractory Urgency Urinary Incontinence. *J Urol*, **198**: 890, 2017
49. Amundsen, C. L., Richter, H. E., Menefee, S. A. et al.: OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women: A Randomized Clinical Trial. *Jama*, **316**: 1366, 2016
50. Rovner, E., Kennelly, M., Schulte-Baukloh, H. et al.: Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn*, **30**: 556, 2011
51. Mangera, A., Apostolidis, A., Andersson, K. E. et al.: An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. *Eur Urol*, **65**: 981, 2014
52. Radley, S. C., Rosario, D. J., Chapple, C. R. et al.: Conventional and ambulatory urodynamic findings in women with symptoms suggestive of bladder overactivity. *J Urol*, **166**: 2253, 2001
53. Sahai, A., Khan, M. S., Le Gall, N. et al.: Urodynamic assessment of poor responders after botulinum toxin-A treatment for overactive bladder. *Urology*, **71**: 455, 2008
54. Sahai, A., Sangster, P., Kalsi, V. et al.: Assessment of urodynamic and detrusor contractility variables in patients with overactive bladder syndrome treated with botulinum toxin-A: is incomplete bladder emptying predictable? *BJU Int*, **103**: 630, 2009
55. Jiang, Y. H., Ong, H. L., Kuo, H. C.: Predictive factors of adverse events after intravesical suburothelial onabotulinumtoxinA injections for overactive bladder syndrome-A real-life practice of 290 cases in a single center. *Neurourol Urodyn*, **36**: 142, 2017
56. Kuo, H. C., Liu, H. T., Chuang, Y. C. et al.: Pilot study of liposome-encapsulated onabotulinumtoxinA for patients with overactive bladder: a single-center study. *Eur Urol*, **65**: 1117, 2014
57. Chuang, Y. C., Tyagi, P., Huang, C. C. et al.: Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes. *J Urol*, **182**: 786, 2009
58. Groen, J., Ruud Bosch, J. L., van Mastrigt, R.: Sacral neuromodulation in women with idiopathic detrusor overactivity incontinence: decreased overactivity but unchanged bladder contraction strength and urethral resistance during voiding. *J Urol*, **175**: 1005, 2006
59. Braun, P. M., Baezner, H., Seif, C. et al.: Alterations of cortical electrical activity in patients with sacral neuromodulator. *Eur Urol*, **41**: 562, 2002
60. Groenendijk, P. M., Heesakkers, J. P., Lycklama, A. N. A. A.: Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? *J Urol*, **178**: 568, 2007
61. Hohenfellner, M., Schultz-Lampel, D., Dahms, S. et al.: Bilateral chronic sacral neuromodulation for treatment of lower urinary tract dysfunction. *J Urol*, **160**: 821, 1998
62. Groenendijk, P. M., Lycklama a Nyeholt, A. A., Heesakkers, J. P. et al.: Urodynamic evaluation of sacral neuromodulation for urge urinary incontinence. *BJU Int*, **101**: 325, 2008

63. Elkelini, M., Hassouna, M. M.: Canadian experience in sacral neuromodulation. *Urol Clin North Am*, **32**: 41, 2005
64. Scheepens, W. A., van Koevinge, G. A., de Bie, R. A. et al.: Urodynamic results of sacral neuromodulation correlate with subjective improvement in patients with an overactive bladder. *Eur Urol*, **43**: 282, 2003
65. Malaguti, S., Spinelli, M., Giardiello, G. et al.: Neurophysiological evidence may predict the outcome of sacral neuromodulation. *J Urol*, **170**: 2323, 2003

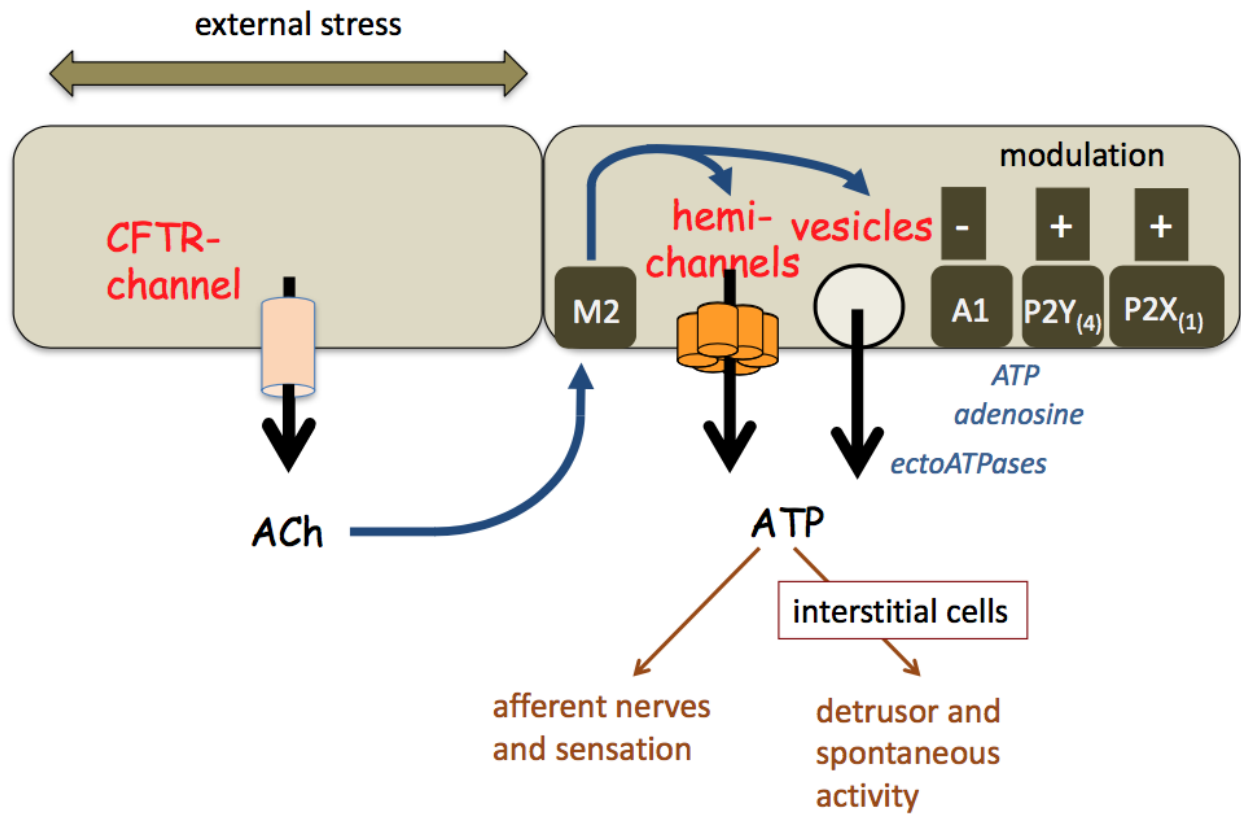


Figure 1. Proposed pathways for stretch-evoked urothelial ATP and acetylcholine (ACh) release according to current experimental data. ACh is importantly (but not exclusively) released via CFTR channels under much lower stresses compared to ATP release. ATP release is increased by muscarinic (M2) receptor activation via routes that include vesicular exocytosis and through connexion hemichannels. ATP may then exert autocrine effects, either directly or via its breakdown products from ectoATPase activity, through purinergic (P2Y or P2X receptors) or adenosine (A1) receptors to modulate further ATP release. ATP may also signal to sensory nerves or interstitial cells in the suburothelium, or even directly to detrusor myocytes. The diagram does not show the role of other modulators of ATP release, such as low pH or variations of trans-urothelial membrane potential – see ref 27 for further details.